Acute renal failure associated with vancomycin and β-lactams for the treatment of osteomyelitis in diabetics: piperacillin–tazobactam as compared with cefepime

R. P. Moenster[1,2], T. W. Linneman[1,2], P. M. Finnegan[1,2], S. Hand[2], Z. Thomas[2] and J. R. McDonald[3]

1) *Pharmacy Service, VA St Louis Health Care System—John Cochran Division,* 2) *Pharmacy Practice, St Louis College of Pharmacy and* 3) *Infectious Diseases, Infectious Diseases Section, VA St Louis Health Care System—John Cochran Division, St Louis, MO, USA*

Abstract

Few data are available on the nephrotoxic potential of vancomycin when combined with certain β-lactam antibiotics for the treatment of osteomyelitis (OM). A retrospective cohort study was conducted of all diabetic patients with OM treated with vancomycin plus piperacillin–tazobactam (VPT) or vancomycin plus cefepime (VC) for at least 72 h at a VA Medical Center between 1 January 2006 and 31 December 2011. All patients with a creatinine clearance (CrCl) of ≤40 mL/min, a blood urea nitrogen/serum creatinine (SCr) ratio of ≥20 : 1 or an absolute neutrophil count of <500 cells/mm^3 were excluded. The primary outcome was development of acute renal failure (ARF), defined as an increase in SCr of 0.5 mg/dL or 50% of baseline. One hundred and thirty-nine patients met the inclusion criteria; 109 in the piperacillin–tazobactam group and 30 in the cefepime group. Among patients receiving VPT, 29.3% (32/109) developed ARF, as compared with 13.3% (4/30) receiving VC (p 0.099). Among patients receiving high-dose therapy (≥18 g of piperacillin–tazobactam daily or ≥3 g of cefepime daily), 37.5% (9/24) receiving VPT and 17.6% (3/17) receiving VC developed ARF (p 0.29). A multiple logistic regression analysis identified weight and average vancomycin trough as the only significant predictors of ARF; the choice of VPT as therapy yielded an OR of 3.45 (95% CI 0.96–12.40; p 0.057). The authors were unable to detect a statistically significant difference in ARF between groups; however, the power requirement was not met. Further study with a larger patient population seems warranted.

Keywords: Acute renal failure, β-lactams, osteomyelitis, vancomycin
Original Submission: 11 June 2013; **Revised Submission:** 20 July 2013; **Accepted:** 23 September 2013
Editor: M. Grobusch
Article published online: 21 November 2013
Clin Microbiol Infect 2014; **20:** O384–O389
doi: 10.1111/1469-0691.12410

Corresponding author: R. P. Moenster, Pharmacy Practice, St Louis College of Pharmacy, 4588 Parkview Place, St Louis, MO 63110, USA
E-mail: **Ryan.Moenster@stlcop.edu**
T. W. Linneman, Pharmacy Practice, St Louis College of Pharmacy, 915 North Grand Boulevard, St Louis, MO 63104, USA
E-mail: **Travis.Linneman@va.gov**

Background

Over 25 million people in the USA are affected by diabetes mellitus. One of the more serious complications of diabetes is osteomyelitis (OM) [1,2]. OM in diabetic patients is often a polymicrobial infection involving Gram-positive organisms (including methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *S. aureus*), *Enterobacteraciae*, and anaerobes [2–4]. Bone biopsy remains the reference standard for diagnosis of OM, but, owing to its invasive nature and complicated growth requirements, is performed less often and/or may not yield helpful results. Because of the frequency of polymicrobial infection and the frequent absence of definitive culture data, patients are often continued on broad-spectrum antibiotic treatment for 4–6 weeks [2,4].

Because of the increasing prevalence of MRSA in both the community and hospital settings, intravenous vancomycin is a common component of therapy for OM [2–5]. In 2009, vancomycin dosing guidelines were released, and called for trough levels of 15–20 mg/L when vancomycin is used to treat

deep-seated infections, such as OM. Vancomycin had been associated with acute renal failure (ARF) in the past, and this was thought to be related to impurities in the early products; however, after adoption of the higher trough goals, increasing rates of vancomycin-associated ARF have been reported in the literature [6–10].

This broad-spectrum empirical treatment for OM often combines vancomycin with an agent active against Gram-negative organisms, such as piperacillin–tazobactam or cefepime [2–7]. As noted, vancomycin may precipitate ARF when given on its own, but there are also data suggesting that rates of ARF with vancomycin increase exponentially when it is administered with certain antibiotics; currently, the best-studied example of this concerns vancomycin and aminoglycosides [11]. Whereas this phenomenon of additive ARF is well documented with vancomycin and aminoglycosides, there is a paucity of data on the potential risk of additive ARF when vancomycin is given with other antibiotics. We set out to compare the potential rates of ARF between two common empirical treatment regimens for OM: vancomycin and piperacillin–tazobactam (VPT), and vancomycin and cefepime (VC).

Materials and Methods

Study design

A retrospective cohort study of all diabetic patients at the VA St Louis Health Care System treated with either VPT or VC for OM between 1 January 2006 and 31 December 2011 was undertaken. Diabetics who received the antibiotics of interest and had ICD-9 code 730.20 underwent chart review to confirm the presence of OM. Inclusion criteria were a diagnosis of diabetes, a diagnosis of OM with a determination to treat by an infectious diseases physician, and treatment with either VPT or VC for at least 72 h, all confirmed by chart review. Patients were excluded if their baseline creatinine clearance (CrCl) was $\leq$40 mL/min, their baseline blood urea nitrogen/serum creatinine (SCr) ratio was $\geq$20:1, or their baseline absolute neutrophil count was <500 cells/mm^3. Additionally, patients could not have received therapy with intravenous acyclovir, amphotericin B, any aminoglycoside or any vasopressor concurrently or within 48 h of antibiotic initiation. Patients were also stratified into high-dose or non-high-dose therapy (high-dose therapy defined as $\geq$3 g of cefepime per 24 h, or $\geq$18 g of piperacillin–tazobactam per 24 h). The primary outcome of the study was the rate of ARF, defined as an increase in baseline SCr of 50% or 0.5 mg/dL between the two groups of patients.

To determine whether patients developed ARF, baseline and peak SCr and blood urea nitrogen were measured, and the baseline and nadir CrCl were calculated with the Cockroft–Gault method. Additional data collected included site of the index case of OM, culture data, prior diagnosis of OM (yes or no), the β-lactam used and the dose, the total duration of combination therapy, time to peak SCr (in days), haemoglobin A1Cs within 6 months of therapy initiation and within 6 months of discontinuation, average vancomycin troughs (calculated by adding all appropriate troughs and dividing by the total number), receipt of loop diuretics, angiotensin-converting enzyme (ACE) inhibitors or contrast dye while hospitalized for the index case of OM (yes or no), total hospital days, and whether or not amputation was required as a part of treatment. Because all patients were followed longitudinally by the infectious diseases team at the VA St Louis Health Care System, both outpatient laboratory data and inpatient data were available and used in this analysis.

Statistical analysis

In order to detect a 19% difference between groups and achieve a power of 80%, a total of 400 patients (200 patients treated with VPT and 200 treated with VC) were needed. The chi-square test or Fisher's exact test was used to compare all non-parametric data, and Student's *t*-test was used to evaluate parametric data; an alpha level of <0.05 was considered to be statistically significant. Additionally, a multivariate logistic regression analysis, considering the variables of age, weight, total duration of therapy, use of a loop diuretic, ACE inhibitor or contrast dye while hospitalized, average vancomycin troughs, the choice of β-lactam, and whether or not the patient received high-dose therapy, was performed to assess independent risk factors for the development of ARF.

Results

A total of 139 diabetic patients with OM were included in the study. Of these, 109 patients received VPT and 30 patients received VC. High-dose therapy was administered to 32 VPT patients and 17 VC patients. Baseline characteristics are shown in Table 1, and were generally similar between groups, with the exception of age, loop diuretic administration during hospitalization, contrast dye administration during hospitalization, and average CrCl nadir.

Overall, 25.9% (36/139) of all patients developed ARF. Thirty-three per cent (12/36) of patients who developed ARF received high-dose β-lactam therapy, as compared with 28.1% (29/103) of patients who did not develop ARF (p 0.001). There were no statistically significant differences between average total duration, average vancomycin troughs or the use of loop diuretics, ACE inhibitors or contrast dye between patients

TABLE 1. Patient characteristics

	Vancomycin + P/T (*n* = 109)	Vancomycin + cefepime (*n* = 30)	p
Average age (years)	62.8	58.4	0.03
Receiving high-dose therapy, % (*n*)	22 (24)	56.6 (17)	<0.05
Previous case(s) of OM, % (*n*)	44 (48)	53.3 (16)	0.39
Average haemoglobin A1c within 6 months of therapy initiation (%)	7.6	7.2	0.55
Average haemoglobin A1c within 6 months after therapy discontinuation (%)	6.6	4.9	0.05
Loop diuretics given during hospitalization, % (*n*)	22.9 (25)	46.6 (14)	0.008
ACE inhibitors given during hospitalization, % (*n*)	55 (60)	50 (15)	0.34
Contrast dye given during hospitalization, % (*n*)	12.8 (14)	10 (3)	0.036
Average CrCl at initiation (mL/min)	72	80.2	0.06
Average CrCl nadir (mL/min)	55.2	69	0.003
Average time to peak SCr (days)	6.60	6.38	0.87
Average duration of combination therapy (days)	14.7	11.3	0.19
Average vancomycin trough (mg/L)	15.8	14.5	0.48

ACE, angiotensin-converting enzyme; CrCl, creatinine clearance; OM, osteomyelitis; P/T, piperacillin–tazobactam; SCr serum creatinine.

who developed ARF and those who did not (specific values are shown in Table 2).

Rates of ARF by β-lactam, those receiving high-dose therapy and by average vancomycin trough are shown in Fig. 1. ARF occurred in 29.3% (32/109) of VPT patients and in 13.3% (4/30) of VC patients (p 0.09). Among patients receiving high-dose β-lactam therapy, with average vancomycin troughs of <16 mg/L, of between 16 and 19 mg/L, and of >19 mg/L, ARF occurred in more patients receiving VPT than receiving VC, but the differences were not statistically significant.

Results from the multivariate logistic regression analysis are shown in Table 3. The six variables reported in Table 3 (age, weight, total duration of therapy, average vancomycin trough, choice of piperacillin–tazobactam as the β-lactam, and the use of high-dose therapy) were determined, by univariate analysis, to be the most likely to affect rates of ARF. In the final multivariate regression analysis, only weight and average vancomycin trough were found to have a significant impact on the development of ARF. The use of high-dose β-lactam therapy did not affect the likelihood of ARF developing. The choice of piperacillin–tazobactam as the β-lactam agent increased the likelihood of ARF developing, but this finding was not statistically signficant.

TABLE 2. Characteristics of all patients with acute renal failure

	Acute renal failure *N* = 36	No acute renal failure *N* = 103	p
Average haemoglobin A1c within 6 months of therapy initiation (%)	7.9	7.3	0.31
Average haemoglobin A1c within 6 months after therapy discontinuation (%)	6.7	6.1	0.29
High-dose therapy, % (*n*)	33.3 (12)	28.1 (29)	0.001
Average total duration (days)	17.6	13.2	0.15
Average vancomycin trough (mg/L)	18.6	14.4	0.05
Given loop diuretics, % (*n*)	25 (9)	29.1 (30)	0.43
Given ACE inhibitors, % (*n*)	55.5 (20)	53.4 (55)	0.36
Given contrast dye, % (*n*)	13.8 (5)	11.6 (12)	0.05

ACE, angiotensin-converting enzyme.

Discussion

This study compared the rates of ARF between diabetic patients with OM who received treatment with VPT and those who received treatment with VC. Although all three agents are extensively cleared through the kidneys, it appeared that patients treated with VPT experienced a higher rate of ARF; however, this difference was not statistically significant (29.3% vs. 13.3%; p 0.09). A non-significant difference was also observed in patients receiving high-dose therapy (31.2% vs. 17.6%; p 0.49). When average vancomycin troughs were taken into account, there was a non-significant, higher rate of ARF patients receiving VPT, regardless of whether the average trough was <16 or >19 mg/L. In a multivariate logistic regression analysis, administration of contrast dye during hospitalization, administration of an ACE inhibitor or receipt of a loop diuretic did not affect a patient's risk of developing ARF. Although not significant, the OR for choice of piperacillin–tazobactam as a β-lactam was 3.45 (95% CI 0.96–12.4). Although the present study was unable to demonstrate a significant difference in the incidence of ARF between the two different combinations, in the overall group, and in each subgroup, there was a consistently higher rate of ARF among patients receiving VPT.

With the publication of vancomycin dosing guidelines endorsing higher trough goals for many infections, retrospective reports have now been published indicating that these higher trough goals may be leading to higher rates of nephrotoxicity in patients receiving vancomycin. A study conducted by Jeffres *et al.* [12] that retrospectively evaluated all patients admitted to a large, tertiary-care hospital over a 6.5-year period who received vancomycin for bronchoalveolar lavage confirmed MRSA healthcare-associated pneumonia. Of the 94 patients included in the study, 42.6% of them developed nephrotoxicity; multiple regression analysis identified troughs ≥15 mg/L as an independent risk factor for developing nephrotoxicity [12]. In 2010, Hermsen *et al.* [9] evaluated patients receiving vancomycin for MRSA pneumonia, endocarditis or OM over a 2-year period, and stratified them by mean

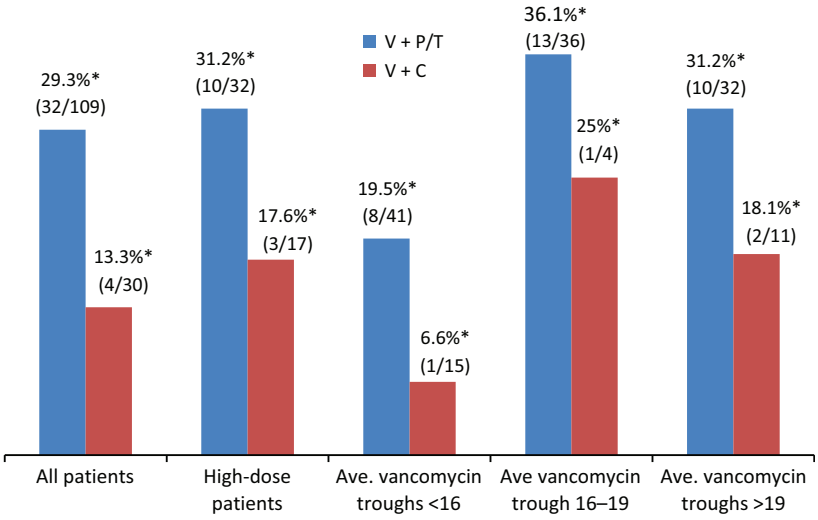

FIG. 1. Frequency of acute renal failure by group. *No differences between V + P/T and V + C were found to be statistically significant. Comparisons across groups were not made. C, cefepime; P/T, piperacillin–tazobactam; V, vancomycin.

TABLE 3. Logistic regression analysis

Parameter	OR	95% CI	p
Age	1.03	0.98–1.08	0.18
Weight (kg)	1.02	1.00–1.03	0.02
Total duration (days)	1.01	0.99–1.04	0.23
Average vancomycin trough	1.07	1.0–1.14	0.02
Choice of piperacillin–tazobactam	3.45	0.96–12.4	0.06
High-dose therapy	1.45	0.56–3.74	0.45

vancomycin trough (<15 mg/L or ≥15 mg/L); nephrotoxicity occurred in 10% of patients with lower troughs and in 31% of patients with higher troughs (p 0.04) [9]. More recently, Horey *et al.* [13] conducted a retrospective chart review of 270 patients within a single Veterans Affairs Medical Center who received vancomycin. The overall incidence of nephrotoxicity in their evaluation was 12.6% (34/270), but a multivariate logistic regression analysis revealed an OR of 1.14 for every 1 mg/L increase in the vancomycin trough; only 7.4% of patients in this evaluation were being treated for bone or joint infections [13]. In an effort to pull together all of the information gleaned from recent studies, Van Hal *et al.* [14] recently completed a meta-analysis of all studies from January 1995 to April 2012 that evaluated vancomycin nephrotoxicity and stratified troughs to <15 or ≥15 mg/L. Fifteen studies met the author's inclusion criteria, and they calculated an overall OR of developing ARF of 2.67 (95% CI 1.95–3.65, p <0.01) for patients with average vancomycin troughs of ≥15 mg/L [14].

Although it appears that vancomycin alone, particularly when efforts are made to achieve trough levels in the 15–20 mg/L range, is nephrotoxic, there are established data showing that vancomycin's nephrotoxic potential can be increased when it is combined with certain antimicrobials. One of the most well-studied examples is the addition of aminoglycosides to vancomycin [6]. In a study conducted by Rybak *et al.* [11], groups receiving vancomycin or aminoglycosides alone, or in combination, were prospectively observed; nephrotoxicity occurred in 5%, 11%, and 22%, respectively (p <0.0001). These results demonstrated that vancomycin combined with an aminoglycoside could be four times as nephrotoxic as vancomycin alone [11].

Few studies are available that have specifically evaluated renal dysfunction in the setting of administration of piperacillin–tazobactam, with or without vancomycin. Although it was not specifically designed to evaluate causation, a recent study was conducted of kidney failure related to broad-spectrum antibiotic use in an intensive-care unit setting [15]. Utilizing a multiple-effects model, the authors found that piperacillin–tazobactam use was associated with the lowest rate of renal recovery of all antibiotics used (more persistent renal failure), and that discontinuation of piperacillin–tazobactam led to an increased renal recovery rate in these patients [15].

Data from randomized controlled trials are limited, and, of those available, some do not specifically concern renal function changes. In evaluations of the use of piperacillin–tazobactam for the treatment of pneumonia or perotinitis, reported rates of renal failure or renal function changes are generally low, and clinically significant differences between comparator agents have not been detected [16–19].

When evaluated for the treatment of diabetic foot infections with a mean treatment duration of 21–24 days, piperacillin–tazobactam led to ARF, defined as an elevated SCr level above the upper limit of normal, in six of 30 (20%) of patients vs. one of 32 (3.1%) of patients receiving imipenem–cilastatin [20].

Although evidence is lacking to suggest that either component (piperacillin or tazobactam) alone, or in combination, is associated with an increased risk of ARF, renal protection in certain cases has been associated with piperacillin use. Animal model data suggest that it may attenuate the renal damage

associated with cisplatin and aminoglycosides; however, the observed benefits could be attributable to the sodium content of the product [21–23].

Numerous studies have been conducted evaluating cefepime's efficacy in the treatment of resistant Gram-negative infections, but there is a paucity of data directly concerning the drug's role in the development of ARF. Yamamura *et al.* [24] examined cefepime vs. piperacillin–gentamicin in patients with febrile neutropenia [24]. ARF was also evaluated, and was found to occur in 15% of patients treated with piperacillin–gentamicin; no cases were reported in the group treated with cefepime [24]. A meta-analysis conducted by Yahav *et al.* [25] included trials evaluating both the efficacy and the safety of cefepime, and the safety analysis, across a number of trials, found no evidence for ARF being associated with the use of cefepime [25]. The available data, although limited, suggest that cefepime alone, or in combination with other antibiotics, has a low potential to increase the risk of ARF.

To the authors' knowledge, no published study has directly compared rates of ARF between patients treated with VPT and those treated with VC. Regarding the rates of ARF for each individual agent, the results reported here seem to agree with the literature. Striving for trough goals of 15–20 mg/L in vancomycin-treated patients has been shown to increase the rates of ARF; however, in the population evaluated here, even though similar average troughs were reported for both groups, more patients treated with VPT developed ARF than those treated with VC. There are limited data on cefepime's nephrotoxic potential, but the available information suggests that it is negligible. In at least one study, piperacillin alone was found to be somewhat renal-protective when given with known nephrotoxins, but rates of ARF were 20% when piperacillin–tazobactam was given for 21–24 days to patients with diabetic foot infections. It is impossible to ascertain causation from a retrospective study such as this, but both these results and the available literature suggest an interaction between aggressive dosing with vancomycin, piperacillin and tazobactam and higher rates of ARF.

The present study is not without limitations. Although we were unable to achieve our power, and this evaluation is probably subject to type II error, we did observe a higher rate of ARF in all patient subgroups treated with VPT than in those receving VC. This study was also retrospective, and involved patients from only one VA Medical Center. However, the study population was quite homogeneous: all were diabetics being treated for OM. We feel that the longer duration of exposure to combination therapy required to treat OM was a strength of this study; shorter durations of treatment may not allow enough exposure time for elevations in rates of ARF to be observed. An additional strength of the evaluation was the inclusion of only patients with stable baseline renal function, and controlling for the most common confounders of renal function (use of ACE inhibitors, loop diuretics, and contrast dye). The design of this study could be improved by including more sites to help bolster the number of cefepime-treated patients.

In conclusion, no statistically significant difference in the rates of ARF between diabetic patients being treated for OM with VPT or VC were observed in this study. In each patient subgroup, however, more VPT-treated patients did develop ARF. Power was not achieved in the VC group; therefore, given that no statistically significant difference was found, this evaluation carries a higher probability of type II error. We believe that further study in this area, involving larger groups and/or multiple sites, is warranted.

Funding

This work was supported by an unrestricted Faculty Research Incentive Fund Grant from the St Louis College of Pharmacy, St Louis, MO, USA.

Acknowledgements

The authors would like to thank G. Zoa, from Washington University in St Louis School of Medicine, for assisting with our statistical analysis.

Transparency Declaration

None of the authors have any conflicts of interest.

References

1. Diabetes.org. Diabetes statistics. Available from: http://www.diabetes.org/diabetes-basics/diabetes-statistics (last accessed 3 September 2011).
2. Hartemann-Heurtier A, Senneville E. Diabetic foot osteomyelitis. *Diabete Metab* 2008; 34: 87–95.
3. Nicolau DP, Stein GE. Therapeutic options for diabetic foot infections: a review with an emphasis on tissue penetration characteristics. *J Am Podiatr Med Assoc* 2010; 100: 52–63.
4. Rao N, Ziran BH, Lipsky BA. Treating osteomyelitis: antibiotics and surgery. *Plast Reconstr Surg* 2011; 127(suppl 1): 177S–187S.
5. Lipsky BA, Berendt AR, Deery HG *et al.* Diagnosis and treatment of diabetic foot infections. *Clin Infect Dis* 2004; 39: 885–910.
6. Wong-Beringer A, Joo J, Tse E, Beringer P. Vancomycin-associated nephrotoxicity: a critical appraisal of risk with high-dose therapy. *Int J Antimicrob Agents* 2011; 37: 95–101.

7. Appel GB, Given DB, Levine LR, Cooper GL. Vancomycin and the kidney. *Am J Kidney Dis* 1986; 8: 75–80.
8. Rybak M, Lomaestro B, Rotschaefer JC *et al.* Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-Systems Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm* 2009; 66: 82–98.
9. Hermsen ED, Hanson M, Sankaranarayanan J, Stoner J, Forescu MC, Rupp ME. Clinical outcomes and nephrotoxicity associated with vancomycin trough concentrations during treatment of deep-seated infections. *Expert Opin Drug Saf* 2010; 9: 9–14.
10. Pritchard L, Baker C, Leggett J, Sehdev P, Brown A, Bayley KB. Increasing vancomycin serum trough concentrations and incidence of nephrotoxicity. *Am J Med* 2010; 123: 1143–1149.
11. Rybak MJ, Albrecht LM, Boike SC, Chandrasekar PH. Nephrotoxicity of vancomycin alone and with an aminoglycoside. *J Antimicrob Chemother* 1990; 25: 679–687.
12. Jeffres MN, Isakow W, Doherty JA, Micek ST, Kollef MH. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant *Staphylococcus aureus* pneumonia. *Clin Ther* 2007; 29: 1107–1115.
13. Horey A, Mergenhagen KA, Mattappallil A. The relationship of nephrotoxicity to vancomycin trough serum concentrations in a veteran's population: a retrospective analysis. *Ann Pharmacother* 2012; 46: 1477–1483.
14. Van Hal SJ, Paterson DL, Lodise TP. Vancomycin-induced nephrotoxicity in troughs of '15–20' mcg/mL era: a systematic review and meta-analysis. *Antimicrob Agents Chemother* 2012; doi:10.1128/AAC.01568-12.
15. Jensen JU, Hein L, Lundgren B *et al.* Kidney failure related to broad-spectrum antibiotics in critically ill patients: secondary end point results from a 1200 patient randomized trial. *BMJ Open* 2012; 2: e000635.
16. Schmitt DV, Leitner E, Welte T, Lode H. Piperacillin/tazobactam versus imipenem/cilastatin in the treatment of nosocomial pneumonia—a double blind prospective multicentre study. *Infection* 2006; 34: 127–134.
17. Brun-Buisson C, Sollet JB, Schweich H, Briere S, Petit C. Treatment of ventilator-associated pneumonia with piperacillin–tazobactam/amikacin versus ceftazidime/amikacin: a multicenter, randomized controlled trial. *Clin Infect Dis* 1998; 26: 346–354.
18. Jaccard C, Troillet CJ, Harbarth S *et al.* Prospective randomized comparison of imipenem–cilastatin and piperacillin–tazobactam in nosocomial pneumonia or peritonitis. *Antimicrob Agents Chemother* 1998; 42: 2966–2972.
19. Alvarez-Lerma F, Insausti-Ordenana J, Jorda-Marcos R *et al.* Efficacy and tolerability of piperacillin/tazobactam versus ceftazidime in association with amikacin for treating nosocomial pneumonia in intensive care patients: a prospective randomized multicenter trial. *Intensive Care Med* 2001; 27: 493–502.
20. Saltoglu N, Dalkiran A, Tetiker T *et al.* Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital. *Clin Microbiol Infect* 2010; 16: 1252–1257.
21. Sabra R, Branch RA. Role of sodium in protection by extended-spectrum penicillins against tobramycin-induced nephrotoxicity. *Antimicrob Agents Chemother* 1990; 34: 1020–1025.
22. Hayashi T, Watanabe Y, Kumano K *et al.* Protective effect of piperacillin against the nephrotoxicity of cisplatin in rats. *Antimicrob Agents Chemother* 1989; 33: 513–518.
23. Santos Navarro M, Zarzuelo Castaneda A, Lopez FG, Sanchez Navarro A, Arevalo M, Lanao JM. Pharmacokinetic parameters of netilmicin and protective effect of piperacillin regarding nephrotoxicity caused by netilmicin. *Eur J Drug Metab Pharmacokinet* 1998; 23: 143–147.
24. Yamamura D, Gucalp R, Carlisle P, Cimino M, Roberts J, Rotstein C. Open randomized study of cefepime versus piperacillin–gentamicin for treatment of febrile neutropenic cancer patients. *Antimicrob Agents Chemother* 1997; 41: 1704–1708.
25. Yahav D, Paul M, Fraser A, Sarid N, Leibovici L. Efficacy and safety of cefepime: a systematic review and meta-analysis. *Lancet Infect Dis* 2007; 7: 338–348.